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ORIGINAL ARTICLE

The Effect of Valproic Acid and Levetiracetam on Bone Metabolism in Children with Epilepsy

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ABSTRACT

Background: Epilepsy is not an uncommon neurological condition among Egyptian children. Early diagnosis of bone metabolism abnormalities in epileptic children using biochemical markers could be a valuable issue. One of these markers is the total serum vitamin D level which can provide a novel insight into the pathogenesis of bone metabolism disorders. The aim of the work was to explore the function of total serum vitamin D in children with epilepsy receiving valproic acid or levetiracetam or both and to correlate lowered level with development of bone metabolism disorders.

Methods: This case-control study was conducted at Zagazig University's paediatric neurology and endocrinology center and paediatric outpatient clinic on 70 children. Patients were divided into control group which included 35 children with epilepsy as a control group and case group which included 35 children with epilepsy subdivided into 3 subgroups according to the type of treatment; BI:10 patients received Navalporate, BII: 10 patients received levatiracetam and BIII: 15 patients received both of Navalporate+ levatiracetam. All patients were subjected to laboratory and X ray investigations.

Results: There is a statistically significant difference between the control group and the other investigated groups. The case group had significantly lower levels of vitamin D. Statistically, there is a significant difference between the studied groups concerning osteopenia changes which was significantly higher in case group (40%) than control group (0%). There is no statistically significant difference between the treatment groups regarding osteopenia changes.

Conclusions: Antiepileptic medicines had a deleterious impact on bone health, with no discernible differences between LEV and VPA.

Keywords: Valproic Acid; Levetiracetam; Bone Metabolism; Epilepsy.

INTRODUCTION

Epilepsy is a condition of the brain characterised by aberrant electrical activity that causes seizures or odd behavior, sensations, and even loss of awareness. It has neurological, cognitive, psychological, and social repercussions and contributes significantly to the global disease load**.** Epilepsy is defined as a brain illness manifested by any of the following symptoms: at least two unprovoked (or reflex) seizures occurring >24 h apart, one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, and diagnosis of an epilepsy syndrome. A provoked seizure is one that happens in response to an acute and temporary cerebral state. They include, but are not limited to, head trauma, intracranial infections following a stroke, acute metabolic disturbances (e.g., hypoglycemia, anoxia), and acute drug or toxin intoxication [1,2].

The majority of children with epilepsy receive drug treatment as their primary type of treatment. The choice of AEDs for a child relies on the type of seizures, the associated symptoms, the patient's age, and the bad effects that result. The primary objective of treating epilepsy is to minimise or eliminate the number of seizures. The treatment of epileptic seizures is reduced to long-term antiepileptic medication use. This family of medications includes pharmaceuticals such as valproate (valproic acid), lamotrigine, phenobarbital, levetiracetam, carbamazepine, and

phenytoin. The inhibition of activating neurons is a potential mechanism of action for medicines in this class. To achieve a condition of remission, when seizures become less or less pronounced, it is important to reach the level of effective concentration of medications in blood plasma [3,4].

Vitamin D is essential for human health and disorders such as cancer, cardiovascular disease, osteoporosis, osteomalacia, the immunological system, and the brain system. In the neurological system, vitamin D can impact proliferation; it also plays a crucial role in neurotransmission and neuroplasticity; and in some situations, it has been claimed that vitamin D can provide neuroprotection by lowering oxidative stress [5].

Anticonvulsants such as carbamazepine, phenytoin, and phenobarbitone are effective inducers of cytochrome P-450 (CYP)-related enzymes; hence, children on long-term anticonvulsants may be at risk for vitamin D deficiency and decreased bone health. These enzymes are involved for 25-hydroxyvitamin D metabolism, turning it into inactive metabolites [6].

Due to its diverse modes of action and broad spectrum of efficacy for a variety of seizure types, valproic acid remains one of the most extensively used AEDs. In addition to its properties, VPA is associated with a variety of undesirable effects. It can affect bone health by its direct influence on bone cells, resistance to the action of parathyroid hormone, inhibition of calcitonin secretion, and improper calcium absorption [7].

Long-term therapy with antiepileptic medications (AEDs) is related with decreased bone mass and a higher risk of bone fractures. It appears that levetiracetam therapy had no effect on bone density, bone strength, or bone turnover [8]. Hence, we studied the effects of sodium valproate and levetiracetam on bone strength, bone mass, and bone turnover in the present study.

There is an association between vitamin D serum concentrations and the incidence of osteoporosis and hip fracture; therefore, the administration of vitamin D to increase bone mineral density (BMD) is advised for epileptic children treated with valproic acid, levetiracetam, or both [9]. Hence, the purpose of this investigation was to determine the serum total vitamin D in children with epilepsy receiving valproic acid or levetiracetam or both and to correlate lowered level with development of bone metabolism disorders

METHODS

This case control study was carried out in the pediatric neurology and endocrinology unit and pediatric outpatient clinic of Zagazig University Hospitals on 70 children attending pediatric inpatient and outpatient clinic during the period during the period from 2022 to 2023. Before starting the study, this study was authorised by the Research Ethics Council of the Faculty of Medicine at Zagazig University Hospitals. After explaining the testing procedures, written informed consent was obtained from every participant. The study was conducted based on The Code (IRB #9494-17-4-2022) of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria included patients from ≥ 2 to ≤ 14 years old at the time of diagnosis who used valproic acid or levetiracetam or both for more than one year. Epilepsy diagnosis according to any of the following condition: at least two unprovoked seizures happening more than 24 hours apart, one unprovoked seizure and approval of additional seizures after two unprovoked seizures occurring during the next ten years and diagnosis of an epilepsy syndrome. A triggered seizure is a seizure that happens in response to an acute neurological disorder [10].

Exclusion criteria were age < 2 or > 14 years old at the time of the initial diagnosis, patients with chronic systemic or neurological illness, patients with malnutrition conditions, patients use vitamin D supplementation and patients who refused to be included in the study.

Patients were divided into two groups; control group (A) which included 35 children with epilepsy as a control group, and group (B) which included 35 children with epilepsy subdivided into 3 subgroups according to the type of treatment: BI included 10 patients received Navalporate, BII included 10 patients received levetiracetam and BIII included 15 patients received both of Navalporate and levatiracetam.

The children participating in the study were submitted to a comprehensive medical history with a focus on duration of treatment with valproic acid or levetiracetam or both, and comprehensive clinical evaluation with an emphasis on anthropometric measurements and neurological examination and signs of vitamin D deficiency. Laboratory investigations were done in the form of total serum vitamin D, calcium, magnisum, phosphorus, parathormone (PTH) and alkaline phosphatase (ALP). X-ray on the upper limb was done.

Statistical Analysis

The data were then imported for analysis into the Statistical Package for the Social Sciences (SPSS version 20.0). The ANOVA, t test, chi square, and Mann Whitney tests were utilised.

RESULTS

There is no statistically significant difference regarding age or sex between the studied case and control groups. There are statistically significant differences across groups with respect to Z score for weight (scores ≤0 prevailed in 40% within case group versus 20% within control group). There is a statistically significant difference between groups in terms of Z score for height (51.4% of the case group and 17.8% of the control group had Z scores 0) (Table 1).

There is a statistically significant difference between the groups in terms of vitamin D levels, which were significantly lower in the case group (71.4% of control group had normal level versus 37.1% within case group) (Table 2).

Serum concentrations of phosphorus, calcium, and magnesium do not differ statistically amongst the tested groups. In terms of parathyroid hormone, there is a statistically significant difference between the tested groups, with the case group having much greater levels (100% of control group had normal level versus 60% within case group). In terms of alkaline phosphatase, there is a statistically significant difference between the analysed groups, with the case group having much greater levels (100% of the control group had normal levels) versus 60% within case group) (Table 3).

Changes in osteopenia are much higher in the case group, which differs significantly from the control group (40% versus 0% respectively) (Table 4).

Group I included patients receiving depakine, group II included patients receiving levetiracetam, while group III included patients receiving both medications. P1 is the distinction between groups I and II, p2 is the distinction between groups II and III, and p3 is the distinction between groups I and III. Kruskal Wallis test considered $p<0.05$ is statistically significant. There is a statistically non-significant difference between the studied subgroups regarding gender, while there is a significant difference between them regarding age. on pairwise comparison, the difference is significant between group I and II. There is a statistically non-significant difference between the studied subgroups regarding Z scores for weight or height (Table 5).

Regarding calcium, magnesium, phosphorus, vitamin D level, parathyroid hormone, and alkaline phosphatase, there are no statistically significant differences between the studied subgroups. Seven patients within the combined group had severe and very severe vitamin D deficiency versus 0% within groups receiving depakin and levatiracetam. Seven patients (46.7%) within the combined group had high parathyroid hormone versus 40% and 30% within groups receiving depakin and levetiracetam respectively. Seven patients (46.7%) within the combined group had high alkaline phosphatase versus 40% and 30% within groups receiving depakin and levatiracetam respectively (Table 6).

There is no statistically significant difference between the tested subgroups in terms of osteopenia changes on X ray (Table 7).

Table 1: Comparison between the studied groups regarding baseline data.

Parameter	**Case group**	**Control group**	**Z**	**p**
	Median (range)	Median (range)		
Age (year)	7 (5 – 8.75)	6 (3.5 – 7.75)	-1.494	0.135
	N=35 (%)	**N=35 (%)**	χ^2	**p**
Sex:				
Female	18 (51.4%)	15 (42.9%)	0.516	0.473
Male	17 (48.6%)	20 (57.1%)		
Weight:				
≤-1.5	0 (0%)	0 (0%)		
>-1.5, <-0.5	3 (8.6%)	0 (0%)		
-0.5 – 0	11 (31.4%)	7 (20%)		
>0 – 0.5	13 (37.1%)	14 (40%)	4.351	0.037*
>0.5 – 1.5	7 (20%)	13 (37.1%)		
>1.5	1 (2.9%)	1 (2.9%)		
Height:				
≤-1.5	11 (31.4%)	0 (0%)		
>-1.5, <-0.5	3 (8.6%)	3 (8.6%)		
-0.5 – 0	4 (11.4%)	3 (8.6%)		
>0 – 0.5	8 (22.9%)	13 (37.1%)	8.994	0.003*
>0.5 – 1.5	5 (14.3%)	14 (40%)		

Parameter	Case group	Control group	Z	p
>1.5	4 (11.4%)	2 (5.7%)		

Z Mann Whitney test; χ^2Chi square test; IQR interquartile range

Table 2: Comparison between the studied groups regarding vitamin D level.

Parameter	Case group	Control group	Z	p
	Median (range)	Median (range)		
Level	25(15 – 37.5)	40(27.5 – 50)	-3.483	<0.001**
Normal Insufficient Mild deficient Severe deficiency Very severe deficiency	13 (37.1%) 8 (22.9%) 7 (20%) 5 (14.3%) 2 (5.7%)	25 (71.4%) 6 (17.1%) 4 (11.4%) 0 (0%) 0 (0%)	χ^2 11.109	0.001**

Z Mann Whitney test; χ^2Chi square for trend test

Table 3: Comparison between the studied groups regarding serum calcium, phosphorus, magnesium, PTH and ALP levels:

Parameter	Case group	Control group	T	p
	Mean ± SD	Mean ± SD		
Calcium	9.15 ± 0.72	9.45 ± 0.6	-1.874	0.065
Magnesium	2.0 ± 0.32	2.14 ± 0.32	-1.872	0.065
Phosphorus	4.39 ± 1.12	4.83 ± 0.88	-1.828	0.07
PTH	55(40 – 125)	45(40 – 50)	-2.389	0.017*
High Normal	14 (40%) 21 (60%)	0 (0%) 35 (100%)	17.5	<0.001**
ALP	135(100 – 200)	90(70 – 120)	-3.878	<0.001**
High Normal	14 (40%) 21 (60%)	0 (0%) 35 (100%)	17.5	<0.001**

Table 4: Comparison between the studied groups regarding osteopenia changes.

Parameter	Case group	Control group	χ^2	P
	N=35(%)	N=35(%)		
Present Absent	14 (40%) 21 (60%)	0 (0%) 35 (100%)	17.5	<0.001**

χ^2Chi square test

Table 5: Comparison between subgroups regarding demographic data.

	Group I	Group II	Group III	χ^2	p
	N=10(%)	N=10(%)	N=15(%)		
Gender: Female Male	 5 (50%) 5 (50%)	 5 (50%) 5 (50%)	 8 (53.3%) 7 (46.7%)	0.038	0.981
Age (year)	8.75(6.75 – 10)	6(4.75 – 6.25)	7(4 – 10)	6.085	0.048*
Pairwise	P1 0.046*	P2 0.246	P3 >0.999		
Weight: <-0.5 -0.5, 0 0 – 0.5 >0.5 >1.5	 1 (10%) 2 (20%) 4 (40%) 3 (30%) 0 (0%)	 0 (0%) 4 (40%) 4 (40%) 1 (10%) 1 (10%)	 2 (13.3%) 5 (33.3%) 5 (33.3%) 3 (20%) 0 (0%)	0.515	0.473
Height:				0.723	0.395

	Group I	Group II	Group III	χ^2	p
≤-1.5	1(10%)	1(10%)	9(60%)		
>-1.5, <-0.5	1(10%)	1(10%)	1(6.7%)		
-0.5 – 0	3(30%)	1(10%)	0(0%)		
>0 – 0.5	5(50%)	2(20%)	1(6.7%)		
>0.5 – 1.5	0(0%)	3(30%)	2(13.3%)		
>1.5	0(0%)	2(20%)	2(13.3%)		

Table 6: Comparison between subgroups regarding serum calcium, magnesium, phosphorus, vitamin D, PTH and ALP levels:

	Group I	Group II	Group III	F	p
	Mean ±SD	Mean ±SD	Mean ±SD		
Calcium	9.29 ± 0.8	9.22 ± 0.84	9.02 ± 0.59	0.468	0.63
Magnesium	2.11 ± 0.35	2.05 ± 0.31	1.9 ± 0.29	1.587	0.22
Phosphorus	4.52 ± 1.12	4.58 ± 1.12	4.18 ± 1.17	0.457	0.637
Normal Insufficient Mild deficient Severe deficiency Very severe deficiency	4 (40%) 2 (20%) 4 (40%) 0 (0%) 0 (0%)	4 (40%) 3 (30%) 3 (30%) 0 (0%) 0 (0%)	5 (33.3%) 3 (20%) 0 (0%) 5 (33.3%) 2 (13.3%)	15.248	0.054
Vitamin D	26(14.5-46.25)	26(17.75 – 40)	23(14 – 35)	1.022	0.6
Parathyroid: Normal High	 6 (60%) 4 (40%)	 7 (70%) 3 (30%)	 8 (53.3%) 7 (46.7%)	MC	0.914
PTH	45 (38.75-104.25)	52.5 (38.75-112.5)	55 (37 – 250)	0.909	0.635
ALP: Normal High	 6 (60%) 4 (40%)	 7 (70%) 3 (30%)	 8 (53.3%) 7 (46.7%)	MC	0.914
ALP	130 (85 – 197.5)	122.5 (97.5 – 212.5)	140 (100 – 250)	**0.779**	**0.677**

Group I: patients receiving depakine, group II: patients receiving levetiracetam, group III: patients receiving both drugs. F One way ANOVA test

Table 7: Comparison between subgroups regarding osteopenia changes in X ray:

	Group I	Group II	Group III	χ^2	p
	N=10(%)	N=10(%)	N=15(%)		
Changes: No Yes	 6 (60%) 4 (40%)	 7 (70%) 3 (30%)	 8 (53.3%) 7 (46.7%)	MC	0.914

Group I: patients receiving depakine, group II: patients receiving levetiracetam, group III: patients receiving both drugs.

DISCUSSION

This result indicated that there is no statistically significant difference between the examined groups regarding age or sex. In agreement with our study, Guo et al. [11] discovered no statistically significant differences in age or sex across the studied groups. In addition, Serin et al. [12] reported that there was no significant difference between the ages of the patients and control groups. Furthermore, El-Haggar et al. [13] demonstrated that there were not significantly more females than males.

We established that there is a statistically significant variation in Z score for weight between case and control groups (Scores ≤0 prevailed in 40% within case group versus 20% within control group. There is a statistically significant difference between groups regarding Z score for height (Scores ≤0 prevailed in 51.4% within case group versus 17.8% within control group). While there is no statistically significant difference in Z scores for weight or height between the various AEDs subgroups.

This is in agreement with El-Khayat et al. [14] who found that height measurements were

reduced in patients compared to the controls, while weight values were not significantly different. They explained their results by presence of hormonal imbalance which was manifested by reduced post provocation growth hormone levels and IGF-1 levels in their included group of patients. On the other hand, Babayigit et al. [15] and Lee et al. [16] discovered no statistically significant difference in anthropometric measurements between epileptic patients and controls.

According to Serin et al. [12], none of the patients who received AEDs experienced a substantial change in z-scores. Although there was a modest decline in scores in the levatiracetam therapy group, the difference was not determined to be statistically significant.

We demonstrated that there is a statistically significant difference between the case and control groups in terms of vitamin D levels, which were significantly lower in the case group (71.4% of control group had normal level versus 37.1% within case group). In agreement with our study, Fan et al. [17] reported that serum 25(OH) D3 levels in the sick group were lower than those in the control group (P = 0.02). Lee and Yu [18], stated that a greater prevalence of vitamin D insufficiency has been documented in epilepsy patients. Even children with epilepsy who began with adequate vitamin D levels became deficient during follow-up and the duration of treatment.

In disagreement with our study, Papassava et al. [19], demonstrated that serum 25(OH)D levels did not differ between patients and controls before vitamin D administration (23.9 ± 11.5 vs 27.4 ± 13.3 ng/ml respectively). Also, the numbers of patients having 25(OH)D levels lower than 20 ng/ml were not significantly different than those of controls (43.2% vs 27.6% respectively). This may be related to variations in solar exposure and eating habits.

In the present investigation, there is a statistically non-significant difference between the cases and control groups regarding serum phosphorus, calcium or magnesium. In agreement with our study, Babayigit et al. [15], Coppola et al. [20], Serin et al. [12] showed that regarding calcium and phosphoruslevels, the differences between cases and controls was not statistically significant ($p < 0.05$).

We demonstrated that there is a statistically significant difference between the case and control groups in terms of parathyroid hormone, which was significantly elevated in the case group (100% of control group had normal level versus 60% within case group). In agreement with our study, Fan et al. [17] revealed that serum PTH levels in the group of child patients were greater than those in the control group (P = 0.002). However, Caksen et al. [21] exhibited no changes in plasma PTH levels in AED-treated patients. This difference may be due to different techniques of measurement.

We demonstrated that there is a statistically significant difference between the case and control groups in terms of alkaline phosphatase, which was significantly elevated in the case group (100% of control group had normal level versus 60% within case group). In agreement with our study, Fan et al. [17] revealed that the patients' group had a greater serum ALP concentration than the control group. Also, Babayigit et al. [15]; Aksoy et al. [22]; Tekin et al. [23] demonstrated a statistically significant difference in ALP levels between the case and control groups (p = 0.045). In numerous investigations, alkaline phosphatase levels were higher in epileptic patients compared to controls.

In the present study, there is a statistically significant difference between the studied groups in terms of osteopenia alterations, with the case group being much more affected (40%) than control group (0%). On X-ray, there is no statistically significant difference between the AED subgroups in terms of osteopenia alterations. In agreement with our study, Fan et al. [17] reported that osteopenia alterations of the lumbar spine were substantially higher in the patient group compared to the control group (P < 0.0001). In addition, Garip et al. [24], Ustaoglu et al. [25] and Brady et al. [26] revealed that patients with epilepsy have a higher risk of fracture, which is mostly due to deteriorating bone health and increased osteopenia changes.

There is no statistically significant difference between the three subgroups in this study regarding calcium, magnesium, or phosphorus. In agreement with our study, Guo et al. [11] demonstrated that there were no variations in calcium, magnesium, or phosphorus amongst the three groups. Also, El-Haggar et al. [13] demonstrated that there were no significant differences between the groups in terms of calcium, magnesium, and phosphorus.

In the current investigation, there is no statistically significant difference in vitamin D levels across the subgroups. Seven patients in the combined group had severe and very severe vitamin D deficiency, compared to 0% within groups receiving depakin and levatiracetam. This came in agreement with Guo et al. [11] who demonstrated that there were no changes between three groups in terms of bone biochemical markers and vitamin D.

We demonstrated that there is no statistically significant difference in terms of serum parathyroid hormone. Seven patients (46.7%) within the combined group had high parathyroid hormone versus 40% and 30% within groups receiving depakin and levetiracetam respectively. In agreement with our study, Guo et al. [11] demonstrated that the levels of PTH in the three groups were the same. In addition, Serin et al. [12] demonstrated that there was no statistically significant difference in the PTH levels of the patients in the examined groups.

There is no statistically significant difference between the analysed groups in the current investigation regarding alkaline phosphatase. Seven patients (46.7%) within the combined group had high alkaline phosphatase versus 40% and 30% within groups receiving depakin and levetiracetam respectively. In agreement with our study, Serin et al. [12] demonstrated that there was no statistically significant difference in the patients' ALP levels across all groups ($p < 0.05$). Also, Guo et al. [11] and El-Haggar et al. [13] showed that there were no differences among three groups regarding alkaline phosphatatse level.

CONCLUSIONS

This study demonstrated that antiepileptic medications had a detrimental effect on bone health, with no discernible differences in bone loss between valproic acid and levetiracetam. These side effects could be brought on by the dosage, treatment plan, and other issues. Patients with a higher risk of bone loss or fracture must find an appropriate antiepileptic medication with a bone-friendly profile.

Conflict of Interest: None.

Financial Disclosure: None.

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